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LEADING ARTICLES IN THIS NUMBER

Albers-Schönberg Disease. With Report of Two Cases in An Egyptian Family.
M. A. Abboud, M.R.C.P., D.C.H., Z. H. Abdin, M.R.C.P., D.Ch., and O. Alfy, M.D., D.Ch. 131

Is Human Poliomyelitis Caused by An Exogenous Virus? (Continued from April).
Ralph R. Scobey, M.D. 139

A Laboratory Diagnostic Sign for Pertussis.
Robert Cohen, M.D. 151

Pediatrics at the Turn of the Century. Eye Symptoms of Infantile Scurvy.
Irving Snow, M.D. 153

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IS HUMAN POLIOMYELITIS CAUSED BY AN EXOGENOUS VIRUS?

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(*Continued from April issue*)

INCUBATION PERIOD OF HUMAN POLIOMELITIS VERSUS EXPERIMENTAL ANIMAL POLIOMYELITIS

Agreement regarding the incubation period of cases of human poliomyelitis has been based almost entirely on the results of animal experiments with the virus of the disease. It is a well known fact that cases of human poliomyelitis in a home, institution or community occur almost simultaneously and are often described as explosive in character. This fact is typical of the effects of poisoning. On the other hand, where experiments on animals in the laboratory are carried out with the virus, a definite incubation period can be established according to the manner in which the virus is administered, its concentration, and the species of animal that is employed. It has always been difficult to reconcile the fact that human poliomyelitis has a short incubation period of one to three days, according to Wickman[55] and others, where the virus would necessarily have to traverse the natural barriers in order to set up infection in the central nervous system and an incubation period of as long as nine or more days in the experimental disease, where the virus is inoculated directly into the central nervous system.

Multiple cases in families present the nearest approach to the grouping of epidemiologically connected cases. There is no conclusive proof that the disease spreads under such circumstances like a contagious or infectious disease. The cases in these families occur simultaneously as in cases of poisoning. Aycock and Eaton[71] (1925) collected the records of 576 multple cases in 253 families. They found that the proportion of secondary cases is highest on the day of the appearance of the first case, and the proportion tends to diminish steadily as time elapses.

PRECIPITATORS OF HUMAN POLIOMYELITIS

Certain factors appear to be necessary in many cases for precipitating the manifestations of human poliomyelitis. These include: fatigue, chilling, trauma, heat and humidity, operative procedures, or pregnancy. Similar factors are well known precipitators of the manifestations of lead toxicity. Neurological manifestations of lead poisoning, and presumably other poisons, occur more frequently in hot weather than during any other season of the year. Suzuki and Kanako[72] (1924), Fukushima and Matsumato[73] (1928), Blackman[74] (1937), Rappaport and Rubin[75] (1941), and Guannattasio et al.[76] (1951) have all pointed out this fact. It is well known that the neurological manifestations of alcohol poisoning (delirium tremens) can be precipitated by overexertion, exposure, operations, trauma, shock, fright and acute inflammatory disease.

COMPARATIVE PATHOLOGY OF HUMAN VERSUS EXPERIMENTAL ANIMAL POLIOMYELITIS

The differences between human poliomyelitis and the experimental animal disease is definitely shown by the divergence of the pathological lesions in the two diseases. It must be admitted that the pathological lesions in the nervous system of experimental animal poliomyelitis are similar to, if not identical with, those in cases of human poliomyelitis. However, the visceral lesions that occur in cases of human poliomyelitis cannot be reproduced in the experimental animal with the virus regardless of the manner of administration or its concentration. Thus, there are to be found in human poliomyelitis many evidences of pathology besides the presence of a virus and viral reaction. In the stomach there is a very high incidence of submucosal petechial hemorrhage associated with intense congestion of the mucosa. Myocarditis, accompanied by mycardial degeneration, has been found in a high percentage of cases. In the parenchymatous organs, especially the liver and kidneys, there is usually demonstrated degeneration of the sort usually described as cloudy swelling. Landon and Smith[77] (1934)pointed out that the granular degeneration of the parenchymatous cells, as well as fatty degeneration represent toxic changes. They state also that the kidneys in cases of human poliomyelitis

show changes that may be attributed to a general systemic toxemia. In practically all cases of human poliomyelitis there is intense congestion of the blood vessels throughout the body.

The widespread lymphoid hyperplasia found consistently in gross and microscopic autopsy examinations in cases of human poliomyelitis never has been explained on the basis of a virus infection. There is involvement of Peyer's patches and the solitary follicles of the gastro-intestinal tract, mesenteric and retroperitoneal lymph nodes, peribronchial lymph nodes, thymus, malpighian corpuscles of the spleen, tonsils, adenoid tissue of the nose and throat, and the lymph nodes of the neck, axilla, groin, and other parts. Burrows[78] (1931) in a series of about fifty autopsies, noted that the maximum amount of lymphoid hyperplasia was in Peyer's patches and the solitary lymph follicles of the gastro-intestinal tract and the mesenteric lymph nodes. He felt that the nerve tissue changes were secondary to those existing in the lymph channels of this tissue. It is a well known fact that lymphoid hyperplasia can occur as a result of poisons and toxins. Doubtless the lymphoid hyperplasia in human poliomyelitis is an expression on the part of the body to poisons and toxins in which protection is afforded by hyperplasia of its reserve forces, the lymphatic apparatus.

The intense reaction in the gastro-intestinal tract not only explains the reaction to a poison but likewise the clinical manifestations of gastro-intestinal irritation that so frequently occur in cases of human poliomyelitis. Although many workers have postulated that the gastro-intestinal tract is the portal of entry of the poliomyelitis virus into the human body, this never has been proven conclusively. Numerous investigators have failed to infect monkeys when the virus has been administered orally even in high concentration and in no case have the gastro-intestinal tract lesions of human poliomyelitis been duplicated in experimental animals. The virus that is recovered from the feces of human poliomyelitis is probably synthesized or activated within the gastro-intestinal tract and is excreted therefrom without gaining entrance to the body. This conclusion appears to be justified by the failure to infect animals orally, and by the work of Gard[79] of Sweden. Gard's extensive studies suggested that intestinal protein is an avirulent or non-neurotropic varient of the poliomyelitis virus, a normal

inhabitant of the intestines. This intestinal protein (virus), according to Gard, is non-pathogenic, but under the influence of exogenous factors is pathogenic when injected into experimental animals. Further proof that the virus in the intestinal tract does not enter the human body to cause human poliomyelitis is indicated by repeated failures to isolate a virus from the blood stream, although human poliomyelitis is generally considered to be a generalized systemic infection. The isolation of a virus from the blood stream would not necessarily indicate that it gained access to the body from the external environment.

ANTIBODY FORMATION AND HUMAN POLIOMYELITIS

There has been much controversy regarding the interpretation of the presence of poliomyelitis virus neutralizing antibodies in human sera. It is now assumed that these antibodies develop following non-paralytic and probably non-symptomatic infection with the virus during childhood as well as in frank cases of paralytic poliomyelitis. Some workers have tried to prove the contagiousness of human poliomyelitis by demonstrating elevated antibodies in contacts. Other workers have been unable to find the antibodies increased in contacts[80]. Poliomyelitis can develop in the presence of neutralizing antibodies and many patients convalescent from the disease show no antibody. The serums of guinea-pigs and rabbits do not contain neutralizing antibody for monkey passage virus, though it is well known that these animals possess an absolute immunity to the virus. Further, antibodies are found in a high percentage of natives of lands in which poliomyelitis is unknown and paradoxically in a much smaller percentage of the population where the disease occurs in epidemic form. The extent of natural resistance to human poliomyelitis is utterly disproportionate to the quantities of virus which is postulated to be present in the general population by analogy with the results of experimental animal poliomyelitis.

It is noteworthy that the appearance of neutralizing antibodies in the blood after the injection of the poliomyelitis virus is very uncertain evidence of parallel immunity to the natural disease[81]. This fact was shown clearly by Kramer[82], in 1936. He vaccinated a group of children with vaccine and two months later found that 50 per cent had developed neutralizing antibodies. However, in a

parallel uninoculated group of children, 41 per cent had also developed antibodies. Kramer's results were in essential agreement with those of Aycock and Hudson[83], who found an increase of 28.6 per cent of immunes among the vaccinated children in their series as compared with an increase of 22.8 per cent of immunes in the unvaccinated control group. Neither of these writers considered the small difference of any practical value in favor of the vaccinated group.

KOCH'S POSTULATES AND HUMAN POLIOMYELITIS

Koch's first and one of his most important postulates emphasizes that a parasite must be found in *every* case of the disease in order to state that that particular parasite is the cause of the disease. In 1952, there were nearly 58,000 cases diagnosed as poliomyelitis in the United States, 75 per cent of which were paralytic. Attempts to isolate the virus from the excretions were carried out in little more than one per cent. In the remaining 99 per cent, a virus was merely assumed to have been present. That the paralysis in this large group might have had many causes is obvious. It is not to be overlooked that a significant number of spinal cords removed from children dying in the acute stage of poliomyelitis are incapable of producing paralysis after intracerebral inoculation in the monkey.

Korns[84] (1953), N. Y. State Public Health Officer, states that the isolation of the poliomyelitis virus for diagnostic purposes is almost never done and is of little practical value, while at the same time being a very difficult procedure. He points out further that isolation of the poliomyelitis virus from the patient by no means establishes the diagnosis since the virus is widely prevalent in the population during epidemic periods without producing disease. Bell[85], epidemiologist, National Institutes of Health, states that the isolation of a virus from poliomyelitis patients is not a routine or reportable procedure; it is carried out only in conjunction with research studies. Serological tests of acute and convalescent blood specimens, he says, are often of no value for determining the cause of the current infection in poliomyelitis because in this disease the antibodies are usually in good titer at the time of onset of symptoms.

BIOCHEMICAL FACTORS IN HUMAN POLIOMYELITIS

There appear to be certain physiological and chemical factors which seem to be necessary for the development of human poliomyelitis and for the synthesis or activation of the virus. Hormonal imbalance has been suggested as an important factor by a number of writers in predisposing an individual to poliomyelitis. Stern[86] (1911) found that a considerable number of cases of this disease showed some symptoms of Basedow's disease, i.e., goiter, tachycardia, tremor, nervousness, etc. Wynkoop[87] (1916) suggested that human poliomyelitis is a disease caused by negation of glandular efficiency. Draper[88] (1932) noted signs in his patients that tended to point toward endocrine deficiencies. The mothers of these poliomyelitis patients not infrequently had moderate or marked exophthalmos or thyroid enlargement. Inglessi[89] (1932) found hypocholesterolemia in thirty children with poliomyelitis during the acute stage and for some time in the paralytic stage. Jungeblut[90] (1932) suggested that the mass protection enjoyed by the adult human population rests primarily on the normal function of the endocrine balance characteristic of mature age. Later[91] (1935) he stated that the protective action against poliomyelitis probably lies in the normal physiological function of the organism and that the main cause for susceptibility is a hormonal dysfunction. Prophylaxis he suggests must consist mainly in correcting the individual susceptibility on a general physiologic-hygienic basis. Aycock[92] (1940) stated that the susceptibility to poliomyelitis is determined by an inherent endocrinopathy which is largely subclinical. Aycock[93] (1940) found a higher average excretion of estrogenic substance in a group of poliomyelitis patients from one to twenty years after an attack of this disease and noted that there was nothing to indicate that this was a sequel of poliomyelitis. This fact suggested to him that endocrinopathy as a basis of susceptibility does not lie in a simple deficiency in the elaboration of estrogenic substance, but rather in some discrepancy in its economy. Aycock pointed out the frequency with which the paralytic disease tends to parallel certain seasonal and climatic fluctuations in physiologic processes. "Such a correlation suggests," he says, "that susceptibility to paralytic poliomyelitis does not lie in any

fixed anatomical character, but is dependent on some physiological process."

The well known fact that virus activity, as well as the reaction to poisons and toxins, produces chromatolysis in an affected nerve cell indicates the necessity for knowledge of the localization of materials and chemical reactions within the cell. Chromatolysis suggests a shift in the balance of a steady state by differential inhibition or acceleration of complex enzyme-regulated reactions[94]. "In addition to the specific production of chromatolytic changes by toxins and neurotropic viruses, interference with enzyme mechanisms by homonal imbalances or dietary deficiencies might conceivably in extreme cases produce the phenomenon of chromatolysis."[94] Aycock and Foley[95] (1945) stress the fact that motor neurone disease may be brought about by an enhancing or inhibiting action on one or more of the enzyme systems.

A study of the biochemical changes that arise during the course of human poliomyelitis has not been followed adequately, but a few important clues have been reported. One of these consists of the presence of coproporphyrin III in the urine of poliomyelitis patients[96, 97]; another is the appearance in the blood of increased amounts of guanidine.[98, 99]. It is not to be overlooked that both of these chemicals are present in the body in increased amounts in cases of poisoning by a number of toxic agents.

Kaplan et al.[100] (1938-39) described an increase of proteases in the cerebrospinal fluid of cases of human poliomyelitis. Kovacs[101] found (1953) in this disease that there are no changes of acid soluble inorganic phosphorus resulting from the interaction of enzymes and phosphorus-containing organic material in the cerebrospinal fluid. In acute bacterial meningitides, on the other hand, a great increase of phosphorus was usually evident. Kovacs[102] (1953) studied the nucleases in the cerebrospinal fluid in cases of human poliomyelitis and found consistently high values. His findings suggested some direct connection between chromatolysis and ribonuclease activity.

The fact that ascorbic acid[103-105], thiamin[106-113], methylene blue[114], as well as iodine[115] have been successfully employed by some workers in the treatment of human poliomyelitis, suggests that certain

biochemical disturbances within the body during the course of the disease can be corrected with chemotherapy. In the treatment of a case of bulbar poliomyelitis, Eskwith[116] (1951) postulated that dimercaprol (BAL) might be effective because in heavy metal poisoning it combines with the metals and protects certain enzymes —those containing a sulfhydryl group—from combination with the poison and because viruses seem to cause necrosis by destroying or inhibiting certain intracellular enzyme systems. He reasoned that if glutathione and other sulfhydryl containing enzymes and tissue protein can be injured by heavy metals, it seems quite possible that they can combine with and be injured by other substances besides metals. Similarly, it is quite possible, he thought, that since dimercaprol contains two sulfhydryl groups, it may protect the enzymes from these non-metallic toxic agents. Eskwith's patient was a 4½ year old girl who had required a tracheotomy and oxygen therapy and whose clinical course was steadily downhill until the dimercaprol injections were given. At the end of 24 hours after therapy was begun, the patient was clinically improved and consciousness rapidly followed. Eskwith learned subsequently that some work had been done with dimercaprol in relation to neurotropic virus infections in experimental animals and that there was no evidence of its efficacy. This fact appears to confirm the belief that human poliomyelitis and the artifically produced experimental animal disease are two entirely different entities.

EXPERIMENTAL ANIMAL POLIOMYELITIS IN HUMAN BEINGS

Once the poliomyelitis virus is recovered from human and extrahuman sources many diversified experiments can be carried out in the laboratory with experimental animals. The unfortunate thing, however, is that these laboratory experiments on animals are interpreted as being applicable to the human disease from whence the virus was obtained and that unjustified conclusions are drawn.

Realizing that an animal will develop experimental poliomyelitis from a virus introduced into its body in an abnormal manner, one can expect that a human being also can develop poliomyelitis of the experimental animal type under the same conditions. Thus, there is to be found in the medical literature reports of the development of poliomyelitis in technicians[117-120] working in labora-

tories with concentrated forms of the poliomyelitis virus. In these cases the portal of entry of the virus is doubtless an abrasion, scratch, laceration or needle prick. A case of poliomyelitis in a technician[118], which followed the contamination by a virus of a scratch, failed to show at autopsy the pathological lesions characteristic of human poliomyelitis arising in a natural manner. It is significant that in this case the gastro-intestinal tract revealed no lesions and no virus was present in the intestinal contents. Over the past 40 years these are the only reported cases of poliomyelitis developing in laboratory workers.

If humans are injected with a concentrated form of active virus, it is natural to expect that they would develop the same type of poliomyelitis that occurs in experimental animals following the injection of the virus. Actually, this did occur in 1935, when some children who received a poliomyelitis vaccine prepared with the virus obtained from experimental animals developed poliomyelitis; half of them died[121]. Significant facts of great importance in these cases were that the incubation period of 6 to 14 days following the injections corresponds with the incubation period of experimental animal poliomyelitis; the fact that the level of the spinal cord first affected corresponded with the extremity in which the injection was made, i.e., the same limb or the contralateral limb parallels recent observations. It is now known, for example, that poliomyelitis can occur following the injection of toxic antigens during the summer months, i.e., pertussis vaccine and diphtheria toxoid, and that the paralysis occurs in the same limb or the contralateral limb where the antigen is injected.

COMMENT

The evidence never has been strong nor very convincing that an exogenous virus enters the human body to cause poliomyelitis. Consequently, year after year, new concepts are presented and old ones discarded that are intended to show where the virus originates outside the body and to establish its portal of entry into the body. Clearly evident are the facts that there is more to indicate that the virus of poliomyelitis is of endogenous origin.

Whether or not one is of the opinion that a poison or virus, or both, are responsible for human poliomyelitis, it is obvious that the fruit, vegetables, milk, and water used by the poliomyelitis patient prior to his or her illness should be carefully considered. If by

careful inquiry a fruit, vegetable, milk, or water source is found, prevention of other cases of this disease can be brought about by warning the public.

Since a poison or virus will cause damage by disturbing normal chemical relationships within the body, particularly enzyme systems, it is imperative, therefore, to determine what chemical changes take place in human poliomyelitis and how they may be restored to normal. It is at this point that much research can be done. A preventive and therapeutic agent could doubtless be developed to maintain or restore normal chemical relationships within the human body to prevent and cure poliomyelitis. It must be seriously considered that if it were possible with a vaccine to prevent the synthesis or activation of the poliomyelitis virus within the human body, it does not follow that a poisonous or toxic activator would be deprived of its ability to cause neurotoxic damage to the lower motor neurone with resulting paralysis.

SUMMARY

1. The exogenous virus theory of cause of human poliomyelitis fails to explain all facts without exception and cannot be considered to be entirely valid.

2. It is emphasized in this report that the fundamental cause of human poliomyelitis appears to be a poison or toxin and that the virus is synthesized or activated within the human body as a result of the poisoning.

3. There appears to be an intimate relationship between virus diseases and diseases resulting from toxic causes. This fact, illustrated by examples, has been stressed.

4. It is pointed out that the poisonous activating factor in cases of human poliomyelitis can originate from fruits, vegetables, milk, and water during epidemics of this disease.

5. The locality influences, seasonal incidence, simultaneous development of multiple cases in homes, institutions and communities, as well as the visceral lesions and other facts, all indicate the association of a poison or toxin with human poliomyelitis.

6. Normal chemical relationships within the body are disturbed in cases of human poliomyelitis; a preventive and therapeutic agent could doubtless be developed to maintain or restore these relationships and thus prevent and cure the disease.

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